REMARKS

Claims 1-11 were pending. The specification has been amended so that the claim for priority under 35 U.S.C. § 119(e) has been placed in the first sentence rather than its original location. A paragraph supplying the definition of "fragment" has been added. The definition was taken from U.S. Patent Application 08/309,644, which had been incorporated by reference and is therefore, not new matter. The information in the paragraph can be found in the subsequently issued patent, U.S. Patent No. 5,763,190, col. 23, lines 35-45. Claims 28-36 are new claims that limit the fragment of Vpr to consist essentially of amino acids 17-36 and/or 59-84. Claim 37-47 have been added to limit the size of the Vpr fragment to less than 50 amino acids. Support for these claims can be found throughout the original application as filed and the paragraph that has been amended with this amendment which recites the different sizes of fragments. Claims 1, 2-6, 7-11 have been amended to specify that the therapeutic compound is a nucleic acid molecule. An abstract has been supplied on a separate sheet as requested by the Office. Upon entry of this amendment claims 1-11 and 28-47 will be pending.

No new matter has been added.

Priority

The Office alleges that Applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C § 119 (e). Applicants have amended the specification so that the claim for priority is in the first sentence of the application.

Objections

Claim 7 stands objected because it is unclear whether a change in the claim was an inadvertent error or an intentional amendment. Applicants have amended claim 7 to remove the inadvertent error, rendering this objection moot.

The specification stands objected because the application allegedly does not contain an abstract of the disclosure as required by 37 C.F.R. § 1.72(b). Applicants have supplied an abstract on a separate sheet as requested, rendering the objection moot.

Rejections under 35 U.S.C. § 112

Claims 1-11 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Applicants respectfully disagree.

Although claims 1-11 satisfied the requirements under 35 U.S.C. § 112, second paragraph in order to further prosecution applicants have amended claims 5-11 so that the claims are even clearer.

In view of the foregoing, Applicants respectfully request that rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

Rejection under 35 U.S.C. § 102

Claims 1 and 7-9 stand rejected under 35 U.S.C § 102(e) as allegedly anticipated by Cohen *et al.* (U.S. Patent No. 6,043,081, hereinafter the "Cohen reference"). The Office alleges that the Cohen reference discusses a chimeric molecule comprising a HIV-1 Vpr protein or fragment thereof, covalently attached to a therapeutic molecule Applicants respectfully disagree.

The standard for anticipation is one of strict identity. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference, *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984).

Claim 1, as amended recites:

> A conjugated composition comprising a nuclear localization sequence fragment of HIV-1 Vpr comprising amino acid sequence 17-36 and/or amino acid sequence 59-84 conjugated to a therapeutic compound, wherein said therapeutic compound is a nucleic acid molecule.

Thus, claim 1 is claiming a composition that comprises an amino acid portion and a nucleic acid molecule portion. The Cohen reference discusses a composition that is either a protein or a nucleic acid molecule, the Cohen reference ***fails to*** discuss a conjugated composition that comprises both a protein and a nucleic acid molecule.

Therefore, Cohen cannot anticipate claim 1 because Cohen does not recite each limitation of the claim.

Claim 7, as amended, recites:

> A method of delivering a therapeutic compound to the nucleus of a cell comprising the step of:
>
> contacting said cell with a conjugated compound, wherein said therapeutic compound is conjugated to a nuclear localization sequence fragment of HIV-1 Vpr protein comprising amino acid sequence 17-36 and/or amino acid sequence 59-84 of said HIV-1 Vpr protein; wherein said therapeutic compound is a nucleic acid molecule and wherein said conjugated compound is taken up by said cell and localized to the nucleus of said cell.

The Cohen reference does not recite a method of delivering a conjugated compound comprising a protein portion and a nucleic acid portion, wherein the protein comprises a nuclear localization sequence fragment of HIV-1 Vpr protein comprising amino acid sequence 17-36 and or amino acid sequence 59-84. As discussed above, the Cohen reference discloses only a protein or a nucleic acid molecule, not a combination of the two. Therefore, the Cohen reference does not disclose each and every limitation of claims 7-9.

The Cohen reference also fails to anticipate new claims 18-37. Claims 18 and 22 recite a Vpr fragment consisting essentially of 17-36 and/or 59-84. The Cohen references does not teach a conjugated composition comprising a nuclear localization sequence fragment of HIV-1 Vpr consisting essentially of amino acid sequence 17-36 and/or amino acid sequence 59-84. The Cohen references does not refer either explicitly or implicitly residues 17-36 and/or residues 59-84 of Vpr. Therefore, the Cohen reference does not contain each and every element of claims 19-37.

Furthermore, the Cohen reference does not anticipate new claims 27-37. Claims 27-37 recite a Vpr fragment that comprises less than 50 amino acids of Vpr. The Cohen reference does not disclose fragments of Vpr that are less than 50 amino acids. The smallest fragment of Vpr that is discussed is 73 amino acid residues in length. Therefore, the Cohen reference fails to anticipate new claims 27-37.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 102(e) be withdrawn.

Claim 1 and 5-11 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by WO9608970 (hereinafter the "'970 reference"). Applicants respectfully disagree. It is also expected that the '970 reference would be used to reject new claims 18-37 and therefore will be argued as if such rejection had been made.

The Office alleges that the '970 reference discusses a "vpr fragment of less than 95 amino acid residues and embraces fragments that ***inherently*** have the recited sequence fragment(s) of claim 1." (Office Action at page 7, emphasis added). Applicants respectfully disagree that the '970 reference discusses fragments that "inherently" have the recited sequence fragment(s) of claim 1. For a publication or disclosure to inherently anticipate a claimed invention, the disclosure must ***always and absolutely*** describe the fragments that contain the recited sequence fragment(s) of claim 1. There are numerous fragments that can be found in the '970 reference that would ***not*** contain the recited sequence fragments. There is no discussion of residues 17-36 and/or 59-84 and therefore, a person of ordinary skill in the art would not have "at once envisaged" the claimed sequence fragments from the disclosure of the '970 reference. The '970 reference discusses fragments from containing as little as 3 amino acids to 50 amino acids but these fragments would not necessarily and absolutely contain either of the amino acid fragments of Vpr recited in claim 1.

As discussed in previous response, the disclosure of the reference must contain "sufficient specificity" to anticipate the claims. (see, M.P.E.P. § 2131.02 and 2131.03) The '970 reference fails to have sufficient specificity. The '970 reference does not discuss with sufficient specificity the disclosed fragments of the pending claims. Therefore, the '970 reference fails to anticipate the claimed invention.

The Office also alleges:

> the claims as written are claiming the same genus as taught by [the '970 reference]. This is because the skilled artisan cannot make a distinction between the instantly claimed genus and the genus taught by [the '970 reference] from either the structure or the function of the vpr protein or fragments thereof as discussed.

(Office Action, pages 7-8). Applicants respectfully assert that the above statement is incorrect. Applicants are not claiming the same genus as taught by the '970 reference because the '970 reference does not ***inherently*** teach Vpr fragments comprising amino acids 17-36 and/or 59-84. Additionally, the skilled artisan can "make a distinction"

between the claimed invention and what is described in the '970 reference. The skilled artisan can immediately understand that the fragments of the '970 reference ***do not*** necessarily and always comprise amino acids 17-36 and/or 59-84, while the Vpr fragments of the instant invention ***must*** contain amino acids 17-36 and/or 59-84. Furthermore, the fragments in the present application comprise a nuclear localization signal and can transport a compound that is attached to the Vpr fragment to the nucleus of a cell. The fragments in the '970 reference do not always and necessarily perform the same function. The present invention is, therefore, distinct from what is described in the '970 reference and is not anticipated.

WO9608970 also fails to anticipate new claims 18-27. As discussed above claims 18-26 recite a Vpr fragment consisting essentially of amino acid residues 17-36 and/or 59-84. The '970 reference does not discuss or even suggest using a fragment that consists essentially of amino acid residues 17-36 and/or 59-84. Thus, the '970 reference fails to recite each and every element of claims and cannot anticipate claims 18-26.

The '970 reference also fails to anticipate new claims 27-37. Claims 27-37 recite that the fragment of Vpr comprise less than 50 amino acids comprising amino acids 17-36 and/or 59-84. The '970 reference does not discuss Vpr fragments less than 50 amino acids in length comprising amino acids 17-36 and/or 59-84. Fragments that are less than 50 amino acids in length that are discussed in the '970 reference would not always and absolutely comprise amino acids 17-36 and/or 59-84. Without the '970 reference being able to show with "sufficient specificity" that fragments of less than 50 amino acids would comprise amino acids 17-36 and/or 59-84 then the reference ***cannot*** anticipate the claimed invention. Furthermore, as discussed above, one skilled in the art would not be able to immediately envisage fragments of Vpr less than 50 amino acids that would comprise amino acids 17-36 and/or 59-84. Therefore, the '970 reference fails to anticipate claims 27-37.

Thus, in view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1-7, 10, and 11 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over the Cohen reference in view of Katz *et al.* (U.S. Patent No. 6,005,004, hereinafter the "Katz reference") and Zuckermann *et al* (U.S. Patent No. 6,468,986, hereinafter the "Zuckermann reference.").

Claims 1-4 also stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over the '970 reference in further view of the Katz reference and the Zuckermann reference. Applicants respectfully disagree.

As an initial matter Applicants note that in the second rejection under 35 U.S.C. § 103(a) the Office has written U.S. Patent No. 6,232,295 even though the first inventor of the '295 patent is Kayyem, not Zuckerman (see, Office Action at page 8). It is assumed that this was a mistake since the Office stated, "Please note that this rejection is a modification of the previous rejection 'unpatentable over [the '970 reference], and further in view of Katz *et al* and Kayyem *et al.*'" (Office Action, page 10). Therefore, the rejection will be responded to assuming that the Zuckerman reference used in both rejections under 35 U.S.C. § 103(a) are the same.

The pending claims are ***not*** obvious over the above identified references. The present invention relates to a composition that is being used to facilitate nuclear translocation. The pending claims recites fragments of Vpr that comprise amino acid sequence 17-36 and/or amino acid sequence 59-84 conjugated to a nucleic acid molecule and fragments of Vpr that comprise amino acid sequence 17-36 and/or amino acid sequence 59-84, wherein the fragment is less than 50 amino acids, conjugated to a therapeutic compound and methods of using the fragments for delivering compounds into the nucleus. It would not have been obvious from the references identified by the Office to use fragments containing these sequences or to use the fragments of Vpr recited in the claims in methods of delivering therapeutic compounds to the nucleus of a cell. There is no disclosure within any of the references, alone or in combination, to use fragments comprising amino acid sequence 17-36 and/or amino acid sequence 59-84 conjugated to a nucleic acid molecule or with fragments that are less than 50 amino acids conjugated to a therapeutic compound. The Cohen reference, as discussed above, does not discuss the fragments that are recited in the pending claims. There is no motivation to conjugate a Vpr fragment with a nucleic acid molecule in any of the references, alone or in

combination, because such a conjugation was not made and there is no suggestion to make such a composition. Furthermore, there is no suggestion or motivation to within Cohen alone or in combination with the other references to use Vpr fragments that are less than 50 amino acid residues. Additionally, the references do not discuss or suggest delivering compounds (e.g. nucleic acid molecules or therapeutic compounds) to the nucleus as recited in the pending claims.

The selection of these fragments is not obvious from the teachings of the references and was not known until the Applicants invention. Numerous fragments could have been chosen from the Vpr protein sequence and the fragments would not have had the residues recited and/or facilitated the translocation of moieties (e.g. nucleic acid molecules and therapeutic compounds) to the nucleus.

Furthermore, Applicants invention of defining the fragments on Vpr that can be used for nuclear localization and conjugating the fragments to either a nucleic acid molecule or a therapeutic compound was unexpected. These results are described in the present application (see, for example, pages 36-37). The present application states:

> Previously it has been shown that Vpr localizes in the nucleus of infected and transfected cells in the absence of other viral proteins despite the lack of a canonical nuclear localization signal

(Specification, page 37, lines 1-3). Thus, there was no clear understanding how Vpr was transported into the nucleus. It could have been possible that Vpr did not have a nuclear localization fragment(s) within the protein itself. It is only through the present invention that these fragments were identified. There are no teachings within the references presented by the Office that disclose mutating residues within these fragments would inhibit nuclear localization of Vpr and thus could be used as a nuclear transport signal when conjugated to either a nucleic acid molecule or conjugating fragments that are less than 50 amino acids to a therapeutic compound. Therefore, the result of defining and identifying two nuclear localization fragments within Vpr ***was unexpected***. Accordingly, the pending claims are ***not*** obvious.

Additionally, the references fail to motivate a person of ordinary skill in the art to make and the use the present invention. According to the Office the Cohen reference fails to teach a polycationic amino acid sequence in the composition or an antisense oligonucleotide as the therapeutic compound, and fails to teach the ionic bonds between

the polycationic molecule and the nucleic acid (see, Office Action, page 9). However, the Katz and Zuckermann references fail to cure these deficiencies.

Katz discusses lipophilic-polycationic delivery systems. The lipophilic-polycationic delivery system that is described in the Katz reference comprises a biologically acid molecule and an omega-3 fatty acid. The complex may also further comprise a polycationic amino acid chain. As discussed in the Katz reference "A major object of the present invention is to synthesize site-specific biomolecular complexes for the selective transport of a therapeutic, prophylactic and diagnostic agent to the target brain cells." (Katz, Col. 5, lines 43-46). Therefore, the object of the Katz invention is to provide entry into a cell, whereas the presently claimed invention is used to deliver a conjugated composition to the nucleus of a cell, which are distinct objects from one another. A person of ordinary skill in the art would readily understand, that a composition can enter the cell without entering the nucleus. The Katz reference does not teach or even suggest combining Vpr with a polycationic amino acid sequence. There is no suggestion in Katz that a polycationic amino acid sequence can be used without the omega-3 fatty acid present in the composition.

The Zuckermann reference discussed compositions and methods for polynucleotide delivery. The Zuckermann reference fails to cure the deficiencies of either the Cohen, the '970 reference, and the Katz references either alone or combined. As was the case for the Katz reference, the Zuckermann reference discusses a polycationic composition with respect to gaining entry into a cell for a polynucleotide. Associating a polypeptide with a polycationic-nucleic acid complex is only to facilitate the entry of the complex into the cell and lists only specific polypeptides that may aid in entering the cell. The peptides are listed as "Additional agents" that "can facilitate endocytosis of the desired nucleic acids or aid binding of the nucleic acids to the cell surface or both." (Zuckermann *et al*, col. 17, lines 23-27.) In the present invention the polycationic amino acid is not used to facilitate the entry of a nucleic acid into a cell, but rather is used to coordinate a nucleic acid with the Vpr fragment, that is, the polycationic amino acid is working as a "glue." A person of ordinary skill in the art would not have been motivated to use a polycationic amino acid sequence as a "glue" because nothing in Katz or Zuckermann discuss using a polycationic amino acid sequence as a "glue."

Furthermore a person of ordinary skill in the art would not have been motivated to use a polycationic amino acid sequence with a conjugated composition comprising a Vpr fragment comprising amino acid sequence 17-36 and/or 59-84 conjugated to a therapeutic compound, wherein the therapeutic compound is a nucleic acid molecule because the Katz and Zuckermann references do not suggest such a use for polycationic amino acid sequences. Throughout the Katz and Zuckermann references they discuss obtaining entry into a cell, something that is not the subject of the claimed invention. A person of ordinary skill in the art would not have been motivated to combine the references because the purposes of the two inventions are non-analogous.

In establishing a *prima facie* case of obviousness under 35 U.S.C. §103, it is incumbent upon the Examiner to provide a reason why one of ordinary skill in the art would have been led to modify a prior art reference or to combine reference teachings to arrive at the claimed invention. *Ex parte Clapp*, 227 U.S.P.Q. 972 (Bd. Pat. Apages Int. 1985). To this end, the requisite motivation must stem from some teaching, suggestion or inference in the prior art as a whole or from the knowledge generally available to one of ordinary skill in the art and not from appellants' disclosure, see for example, *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 U.S.P.Q.2d 1434 (Fed. Cir. 1988); and *Ex parte Nesbit*, 25 U.S.P.Q.2d 1817, 1819 (Bd. Pat. Apages Int. 1992). In this respect, the following quotation from *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. Apages 1993), is noteworthy:

> Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of the references." ... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent Applicants' invention without also providing evidence of the motivating force that would **impel** one skilled in the art to do what the patent Applicants have done. (citations omitted; emphasis added)

Significantly, as discussed above, the Office Action identifies no "motivating force" that would "impel" persons of ordinary skill to modify the respective teachings of the cited references and achieve the claimed invention.

Rather, the Office Action makes a general statement that it would be obvious to combine teachings of a reference discussing a particular retroviral vector with a reference that discusses a specific promoter. Such a generalized motivation **is not** a "motivating force" that would "impel" persons of ordinary skill to modify the respective teachings of the cited references and achieve the claimed invention. Such a statement, at most, raises an inappropriate "obvious to try" standard. Indeed, the court made it clear that it is improper to reject claims as "obvious to try" where the motivation to combine references arises merely because the subject matter of the claimed invention is a promising field for experimentation, although the prior art provides only general guidance as to particular form of the claimed invention or how to achieve it. *In re O'Farrell*, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988). Without more specific suggestions in the prior art, there is insufficient motivation to combine the cited references. Furthermore, "focusing on the obviousness of substitutions and differences, instead of the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Son*, 16 U.S.P.Q.2d 1923, 1927 (Fed. Cir. 1990).

Therefore, the Office has failed to show any motivation as to why a person of ordinary skill in the art would combine the references Cohen, the '970 reference, Katz and Zuckermann. There is nothing in any of the references that would "impel" one of ordinary skill in the art to make the combination. The Office has also failed to show that a person of ordinary skill in the art would have an expectation of success based on the combination of the references. The Office states, "The ordinary skilled artisan would have been motivated to do so because it was known that the addition of the polycationic molecule would enhance intracellular penetration of the therapeutic compound and reduce the degradation of nucleic acids during the delivery process." (Office Action, at page 10) As an initial matter there is no evidence within the references that the polycationic amino acid molecules would "enhance intracellular penetration." Rather, the polycationic molecules are used to facilitate uptake, after which there is no suggestion

or motivation in Katz or Zuckermann that the polycationic amino acid sequences facilitate any penetration after being taken up by the cell.

However, even if there were evidence for "enhanced intracellular penetration" the Office only uses the above general statement and that there would have been "a reasonable expectation of success" to state that the claimed invention is allegedly *prima facie* obvious. The Office provides no specific reason or evidence as to ***why*** a person of ordinary skill in the art would have an expectation of success. Again, as discussed above, the references would not "impel" one of ordinary skill to make the combination and/or modify the references to obtain the claimed invention. The Office has used nothing more than generalizations to combine the references, which is improper.

In addition, it appears that the only motivation that the Office is using to combine the references is the use of the Applicants' specification and hindsight reconstruction, which is strictly forbidden. *In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."). When assessing whether or not a combination of references would have produced a claimed invention, one must consider the teaching of each reference as a whole without undue emphasis on those features that would support a finding of obviousness. *In re Wesslau*, 147 U.S.P.Q. 391 (C.C.P.A. 1965) (it is impermissible to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what the references fairly suggest to one of ordinary skill in the art).

Consideration of the cited references as a whole for what they each fairly suggest, demonstrates that a person of ordinary skill seeking to combine them would not have produced any claimed invention. In this respect, the Office Action has apparently picked one particular element from Cohen or the '970 reference, one particular element from Katz, and one particular element from Zuckermann. One skilled in the art, however, would ***not*** be motivated to pick and choose only those specific elements referred to in the Office Action from the many elements recited in the references and combine the selected elements in the specific manner indicated in the Office Action. For example, one skilled in the art would not have picked only the polycationic amino acid sequence from reading the Katz reference because if taken in its entirety one skilled in the art would have taken a

composition of an omega-3 fatty acid ***and*** a polycationic amino acid sequence, which contains elements not recited in the present invention. A person of ordinary skill in the art would not expect the composition disclosed in the Katz reference to work without the omega-3 fatty acid and therefore any composition taken from Katz would include the omega-3 fatty acid. Zuckermann does not discuss using a polycationic amino acid sequence with a conjugated composition as is claimed in the present application and therefore there would have been no expectation of success of using polycationic amino acid sequences with a conjugated composition because of the focus in these references on the delivery of polynucleotides into a cell.

Indeed, it appears that the only guide to picking and choosing particular elements from the cited art of records appears to have been the present application. Thus, the combination of references is improper for, at the very least, failure to provide motivation to combine references and for its use of hindsight reconstruction based upon Applicants' disclosure. Furthermore, as discussed above the references either alone or in combination do not suggest or motivate a person of ordinary skill in the art to use the fragments recited in the pending claims.

The Federal Circuit has recently affirmed the requirement for motivation to combine references, stating that:

> virtually all [inventions] are combinations of old elements. Therefore, an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed [**10] elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention . . .
>
> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and ***with no knowledge of the claimed invention***, would select the elements from the cited prior art references for combination in the manner claimed . . .

> To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

Yamanouchi Pharm. Co. v. Danbury Pharm, Inc., 231 F.3d 1339 (Fed. Cir. 2000); 56 U.S.P.Q.2D 1641, 1645, citing *In re Rouffet*, 149 F.3d 1350, 1357-58, 47 USPQ2d 1453, 1457-8 (Fed. Cir. 1998) (emphasis supplied).

It appears that the Office has done what Yamanouchi reaffirms should not be done -- used Applicants' specification as a blueprint.

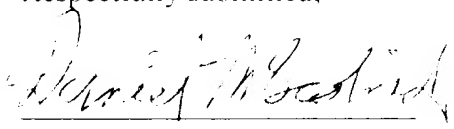
Thus, in view of the foregoing, Applicant respectfully submits that the Office has failed to establish a *prima facie* case of obviousness. In particular, the Office has failed to provide any motivation that would *impel* one skilled in the art to modify and/or combine the cited references so as to produce Applicants' claimed inventions.

Accordingly, Applicants respectfully request the rejection under 35 U.S.C. § 103(a) be withdrawn.

Conclusion

Applicant believes the claims are in condition for allowance. An early Notice of Allowance is therefore earnestly solicited. Applicant invites the Examiner to contact the undersigned at (215) 665-6928 to clarify any unresolved issues raised by this response.

Respectfully submitted,



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